

AMENDMENT

In the Specification:

Please replace the paragraphs on page 15, lines 5-18, with the following:

(M5+TE) was constructed by combining the engineered *NdeI* site from pJRJ10 (Jacobsen, J.R., *et al.*, *Biochem* (1998) 37:4928-4934) with the *EcoRI* site from pCK15 (Cortes-Kao, *supra*). The *Nde-EcoRI* fragment was cloned in pET21c to obtain the expression plasmid pRSG46. Expression constructs for (M2+TE) and (M6+TE) were prepared similarly using an engineered *Nhe* site immediately upstream of the corresponding KS (at position 7570, 5'-GCTAGCGAGCCGATC-3' ^(SEQ ID NO:1) and at position 28710, 5'-GCTAGCGACCCGATC-3' ^(SEQ ID NO:2)).

These constructs were expressed in *E. coli* BL21 (DE3) along with an expression system for *sfp* phosphopantetheinyl transferase from *B. subtilis*. The co-expression is described by Lambalot, R.H., *et al.*, *Chem. Biol.* (1996) 3:923. For the construction of the *sfp* gene, the *NdeI-HindIII* fragment derived from the pUC8-*sfp* (Nakano, M.M., *et al.*, *Mol. Gen. Genet.* (1992) 232:313-321) was cloned into pET28 which has a kanamycin resistance gene to give resultant plasmid pRSG56. The resulting proteins were then isolated for use in the reaction mixtures described in the Examples below.

In the Claims:

Please replace the presently pending claims with the following claims:

23. (Amended) A hybrid modular polyketide synthase (PKS) comprising at least a first naturally occurring extender module and a second naturally occurring extender module of a different PKS from said first module,

wherein the C-terminus of said first module is covalently linked to the N-terminus of a naturally occurring intra-molecular linker (RAL) or inter-molecular linker (ERL) and the N-terminus of the second module is covalently linked to the C-terminus of said RAL or ERL, and

wherein either said first module or second module is not covalently linked to said RAL or ERL in a naturally occurring polyketide synthase;

whereby the transfer of a nascent polyketide chain from said first module to said second module is facilitated.

~~Please cancel claim 24.~~

25. (Amended) The hybrid modular PKS of claim 23 wherein said RAL is selected from the group consisting of M2 *ery*, M4 *ery*, M6 *ery*, M2 *rif*, M3 *rif*, M5 *rif*, M3 *rap*, M4 *rap*, and M7 *rap* intra-module linkers (SEQ. ID. NO's: 3-11, respectively).

B3
Sub C
26. (Amended) The hybrid modular PKS of claim 23 wherein the ERL is selected from the group consisting of M3 *ery*, M5 *ery*, M4 *rif*, M7 *rif*, M8 *rif*, M9 *rif*, M5 *rap*, and M11 *rap* inter-module linkers wherein the portions of said modules coupled to the N-terminus of the succeeding module are represented by SEQ. ID. NO's: 12-19, respectively.

~~Please cancel claim 27.~~

28. (Amended) The hybrid modular polyketide PKS of claim 23 which contains *ery* modules 1 and 3 through 6 inclusive and tylosin module 2, and wherein said polyketide chain is transferred from *ery* module 1 to *tyl* module 2 and then to *ery* modules 3 through 6 inclusive.

Sub E2
29. (Amended) The hybrid modular polyketide PKS of claim 23 which contains *ery* modules 1 through 5 inclusive and narbomycin module 6, wherein said polyketide chain is transferred from *ery* modules 1 through 5 inclusive to *nar* module 6.

B4
30. (Amended) The hybrid modular polyketide PKS of claim 23 which contains modules 1 and 3 through 6 inclusive of *ery* and modules 2-3 of tylosin, spiramycin or niddamycin, wherein said polyketide chain is transferred from *ery* module 1 to modules 2-3 of tylosin, spiramycin or niddamycin and then to *ery* modules 3 through 6 inclusive.

31. (Amended) The hybrid modular polyketide PKS of claim 23 which contains modules 1 through 3 inclusive of tylosin, spiramycin or niddamycin and modules 3 through 6 inclusive of *ery*, and wherein said polyketide chain is transferred from modules 1 through 3 inclusive of said tylosin, spiramycin or niddamycin to *ery* modules 3 through 6 inclusive.

32. (Amended) The hybrid modular polyketide PKS of claim 23 which contains a module of tylosin, spiramycin or niddamycin and modules 1-2 and 3 through 6 inclusive of *ery*,

wherein said polyketide chain is transferred from *ery* modules 1-2 to the tylosin, spiramycin or niddamycin module and then to *ery* modules 3 through 6 inclusive.

33. (Amended) The hybrid modular polyketide PKS of claim 23 which contains modules 1 and 3 through 6 inclusive of *ery* and module 5 of tylosin, spiramycin or niddamycin having the enoyl reductase catalytic activity inactivated, wherein said polyketide chain is transferred from *ery* module 1 to module 5 of tylosin, spiramycin or niddamycin and then to *ery* modules 3 through 6 inclusive.

34. (Amended) The hybrid modular polyketide PKS of claim 23 which contains *ery* modules 1 through 4 inclusive and 6 and module 6 of spiramycin or niddamycin, wherein said polyketide chain is transferred from *ery* modules 1 through 4 inclusive to module 6 of spiramycin or niddamycin and then to *ery* module 6.

35. (Amended) The hybrid modular polyketide PKS of claim 23 which contains module 1 of FK-506 or 520 and modules 2 through 14 inclusive of rapamycin, wherein said polyketide chain is transferred from module 1 of FK-506 or 520 and then to modules 2 through 14 inclusive of rapamycin.

36. (Amended) The hybrid modular polyketide PKS of claim 23 which contains module 1 and 11 through 14 inclusive of rapamycin and modules 2 through 6 inclusive of FK-506 or 520 wherein said polyketide chain is transferred from module 1 of rapamycin to modules 2 through 6 inclusive of FK-506 or 520 and then to modules 11 through 14 inclusive of rapamycin.

37. (Amended) The hybrid modular polyketide PKS of claim 23 which contains module 1 of rapamycin, modules 2 through 7 inclusive of FK-506 or 520 and modules 12 through 14 inclusive of rapamycin, wherein said polyketide chain is transferred from module 1 of rapamycin to modules 2 through 7 inclusive of FK-506 or 520 and then to modules 12 through 14 inclusive of rapamycin.

38. (Amended) The hybrid modular polyketide PKS of claim 23 which contains module 1 of rapamycin, modules 2 through 8 inclusive of FK-506 or 520 and modules 13-14 of rapamycin, wherein said polyketide chain is transferred from module 1 of rapamycin to modules 2 through 8 inclusive of FK-506 or 520 and then to modules 13-14 of rapamycin.

39. (Amended) The hybrid modular polyketide PKS of claim 23 which contains modules 1 through 10 inclusive of rapamycin and modules 7 through 10 inclusive of FK-506 or 520, wherein said polyketide chain is transferred from modules 1 through 10 inclusive of rapamycin to modules 7 through 10 inclusive of FK-506 or 520.

Please cancel claims 40-44.